

MONITORING ANTIVIRAL TREATMENT EFFICACY AND RESISTANCE

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Abstract

The determination of plasma HIV 1 RNA concentrations (viral load), together with changes in CD4 cell counts currently serve as the primary parameters to monitor the efficacy of highly active antiviral treatment regimens (HAART). Incomplete inhibition of HIV 1 replication may result in the emergence of viral isolates expressing reduced susceptibility (resistance) to an administered antiviral drug. For most drugs used in the treatment of HIV 1 infected individuals to date, specific resistance conferring mutations causing reduced susceptibility to the drug, have been identified. The determination of these mutations in clinical isolates may serve as a surrogate for laborious and time consuming drug susceptibility determinations. Several of the mutations have demonstrated to also confer cross resistance to other drugs of the same class and moreover, the mutations may affect the replication capacity of the virus. In general, rather distinct mutation patterns have been observed for each of the inhibitors, in particular for RT inhibitors. The identification of clear resistance mutation patterns in response to protease inhibitors is less clear cut, mainly because long term studies with these drugs are limited and, moreover, because of the high level of genetic flexibility of the protease gene.

For a large number of mutations, their effects on changes in the viral drug susceptibility has been documented. Currently, several methods have been developed to either qualitatively or quantitatively determine the presence of drug resistant mutations. Genotypic HIV 1 resistance measurements together with viral load determinations and drug susceptibility measurement are important tools for the evaluation of antiviral treatment regimens in HIV 1 infected individuals. The presentation reviewed application and constraints of available technologies for genotypic and phenotypic resistance testing.

At present, phenotypic and genotypic resistance determinations are performed mainly by research laboratories and core facilities, without any systematic inter-laboratory standardization or quality control. However, the results of these determinations will be of increasing diagnostic value in a number of clinical settings including resistance monitoring of patients prior to therapy initiation or at the time of therapy failure.

In a first multicenter evaluation of the quality and relative sensitivity of DNA sequence analysis procedures a large number of laboratories worldwide were investigated. Using their standard laboratory methods and technologies, participants analyzed a coded set of plasmid mixtures containing heterogenic nucleotide mixtures at several drug resistance codons and reported both qualitative and quantitative results. The results of this study will be presented, demonstrating that extensive differences we observed in the sensitivity and accuracy of DNA sequence analysis approaches. Today there is a clear tendency towards the use of genotyping assays as diagnostic procedures in clinical practice. Taking this into account, the development of quality control programs for genotyping is essential and may help to improve the overall performance of laboratories.

*Paper not available.